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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,145	09/07/2001	Yasushi Inoue	3274-011309	7911

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	12

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,145	INOUE ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-16 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 3-16, 21-30 are currently pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 3-30 which depend directly or indirectly from claim 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "wherein the translation activity of the modified promoter". It is not clear to the Examiner as to how a promoter can have a "translation activity". A promoter is generally known to "transcribe" leading to the formation of an mRNA from the DNA and it is the ribosomes that "translate" the mRNA information into proteins. Therefore, the above phrase renders the claim indefinite.

Claim 1 and claims 3-30 which depend directly or indirectly from claim 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "promoter of α-amylase in which the sequence having at least one restriction site is absent". The entire phrase in highly unclear to the Examiner in the context of the above claim. It is not clear whether applicants are referring to the "activity" as being absent or the "restriction site" being absent in the modified promoter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-6, 8-16, 21, 23-24, 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an α-amylase promoter DNA with SEQ ID NO:1or 2 or an α amylase promoter DNA isolated from *B.amyloliquefaciens* and modified such that a restriction site is created and at the same time the consensus ribosome binding region and the RNA polymerase binding region are not affected, does not reasonably provide enablement for any modified α-amylase promoter thereof including any variant sequences of SEQ ID NO:1 or 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 3, 5-6, 8-16, 21, 23-24, 26-30 are so broad as to encompass any α-amylase promoter from any source, and vectors and host cells and method of making heterologous polypeptides using such vectors comprising such DNAs. The scope of the claims is not

commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA sequences that are broadly encompassed by the claims.

The applicants propose to use the above polynucleotides for a variety of processes one of which is to make higher amounts of heterologous polypeptides which are expressed through the aid of the promoter activity. Since a specific nucleotide sequence determines associated higher promoter activity leading to the high level expression of the heterologous polypeptide that is linked to the promoter, changing the nucleotide sequences as proposed by the applicants and/or addition of substantial amount of additional nucleotide sequence unrelated to the nucleic acid sequence of SEQ ID NO:1 or 2 may not lead to desired function of the polynucleotides. This is because the changes suggested by the applicants will result in an enormous number of nucleotide sequences that may or may not continue to have the high level of promoter activity. However, in this case the disclosure is limited to the α-amylase promoter isolated from *B.amyloliquefaciens*, and having the nucleotide sequence SEQ ID NO:1 or 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or modifications of nucleotides, as encompassed by the instant claims, and the base changes within a nucleic acid's sequence that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given DNA to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses all modifications and fragments of any α amylase promoter DNA because the specification does

not establish: (A) regions of the promoter DNA sequence which may be modified affecting the above mentioned activity/utility; (B) the general tolerance of the *B.amyloliquefaciens* α amylase DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide of any α-amylase promoter DNA nucleotide with an expectation of obtaining the desired biological function and utility; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any α amylase promoter DNA including recombinants, variants and mutants. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing that claim 1 is amended to specifically recite that the modified promoter is derived from *B.amyloliquefaciens* and that the restriction site is located at least 10 bases from the 3' end. However, such an amendment is not persuasive to overcome the above rejection. This is because claim is still directed to (all) modified promoters with higher activity. Applicants have not taught as to how and which specific positions on the promoter nucleotide bases needs to be changed and changed to which other nucleotide base etc. Such information is still lacking. It is

not plausible for those skilled in the art to conclude that just addition of restriction sites to the 3' end of the promoter increases the activity. While applicants argue that the said promoter is tolerant to modification, such argument of theirs especially with reference to "the data which shows that the modified promoters have over times the enzymatic activity" is highly confusing (see lines 9-12, 2nd para, page 6 of the response). It is not clear to the Examiner as to how promoters can be judged by their enzymatic activity and what specific enzymatic activity this promoter has? Therefore, above claims continues to be non-enabled with respect to the making of the modified promoters. Hence the above rejection is maintained.

Claims 1, 3, 5-6, 8-16, 21, 23-24, 26-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of modified α-amylase promoter DNA molecules including recombinants, variants and mutants.

The specification does not contain any disclosure of the structure of modified α-amylase promoter DNA sequences that are encompassed by the claims. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including variants, mutants, recombinants and partial DNA sequences. The specification discloses only a couple of species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the

claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

There is no arguments by applicants in response to the above rejection. However, Examiner maintains the above rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-6, 8-16, 21-24, 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palva et al. (Gene, 1981, Vol. 15:43-51) and common knowledge in the art regarding the restriction sites sequences. Claims 1, 3, 5-6, 8-16, 21-24, 26-30 are drawn to a promoter of α-amylase gene derived from a Bacillus and having at least one restriction site in the 3'end region and an initiation codon such that the activity of the promoter is higher than that of a promoter without the restriction site, wherein the restriction sites are Bam*H*1, Sma1, KpnI etc. and wherein the promoter sequence forms a part of a vector, wherein a gene encoding a protein is inserted into a restriction site, wherein the protein is an intracellular enzyme and wherein the sequence is a trehalose phosphorylase or a maltose isomerase etc. wherein the expression vector is used to

transform a host microorganism and the protein is produced by culturing the recombinant microorganism.

Palva et al. teach the nucleotide sequence of the α-amylase promoter isolated from *B.amyloliquefaciens*. The reference also teaches that when the promoter and the signal sequence was used to express another gene from another bacillus, the expression was high and efficient. The reference teaches that the amyloliquefaciens α-amylase promoter comprises a sequence which is partially homologous to "Shine-Delgarno" sequence, which is thought to play an important role in ribosome-binding to mRNA and about 30-35 base upstream from the start codon, there are two potential "Pribnow box" sequences which are the potential prokaryotic RNA polymerase binding sites all of which may be responsible for the efficient activity of the promoter (see page 49-50). In particular Palva et al. disclose the Shine-Delgarno sequence 5'-GAG AGG GAG AGG A-3' just 5' to the start of the translation initiation codon. Analyzing this sequence it would be readily evident and obvious to those skilled in the art that the last three nucleotides, "GGA" form the first half of the restriction sequence of BamH1 restriction site, GGATCC.

The restriction site sequences and their presence and advantages in vectors are also common knowledge in the art. The restriction site sequence of BamH1, i.e., GGATCC leading to overhangs is also well known in the art of molecular biology.

Combining such detailed teachings from the Palva et al. reference, and the general knowledge in the art regarding restriction site sequences, it would have been obvious to one of ordinary skill in the art to use the promoter sequence of *B.amyloliquefaciens* and modify it by way of introducing three extra nucleotides TCC such that the promoter sequence would end in

BamH1 restriction site in the 3' end region of the promoter such that the Shine-Delgarno sequence is preserved and any heterologous polynucleotide ending with a BamH1 restriction site could be easily attached to the promoter for the attached gene to be efficiently transcribed. Further, it would have been obvious to one of ordinary skill in the art to put any restriction site after the BamH1 site. However, since BamH1 site preserves the Shine-Delgarno sequence of the promoter, it would have been obvious to introduce additional sites after BamH1 site. With such a construct in hand it would have been obvious to one of ordinary skill to introduce it into a plasmid and make an expression vector for expression of any heterologous protein which can be efficiently expressed in the host cell. One of ordinary skill in the art would have been motivated to do so because Palva et al. disclose that the expression of a protein using the amyloliquefaciens promoter was better than the expression of a heterologous protein using the natural promoter of the specific host cell. One of ordinary skill in the art would have been motivated to express any protein including the phosphorylase and the isomerase enzymes which have industrial importance. One of ordinary skill in the art would have a reasonable expectation of success since Palva et al. provide the promoter sequence and also demonstrate that it is an efficient promoter compared to the natural promoter of a host cell.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that the *B.amyloliquefaciens* α-amylase promoter was isolated a very long time ago and if it was obvious to those skilled in the art to put a restriction site at its 3'end it would have been done so by those skilled in the art. Furthermore, applicants also argue that as Palva et al. teach

the importance of Shine-Delgarno (S-D) and therefore those skilled in the art would not be motivated to change or modify that sequence but rather would be motivated to preserve such sequence to ensure optimal promoter activity. Examiner agrees with the applicants partially. Yes, those skilled in the art would be motivated to preserve the S-D sequence for optimal activity and also at the same time would be motivated to make use of it for subcloning. Therefore, by studying the restriction site sequences of different restriction enzymes and the 3' ending nucleotide sequences it would have been obvious to those skilled in the art that the S-D ends exactly in half the restriction sequence of BamH1 enzyme and that just extending the sequence by three nucleotides TCC, one can create a restriction site at the same time preserve the S-D sequence of the promoter. Therefore, contrary to applicant's argument it would have been *prima facie* obvious to those skilled in the art to make and use the invention as claimed.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao Ph.D.
Patent Examiner, A.U. 1652
9/19/03